

Published in final edited form as:

Neurology. 2008 April 29; 70(18): 1594–1600. doi:10.1212/01.wnl.0000306314.77311.be.

Hippocampal neurochemistry, neuromorphometry, and verbal memory in nondemented older adults

M.E. Zimmerman, PhD, J.W. Pan, MD, PhD, H.P. Hetherington, PhD, M.J. Katz, MPH, J. Verghese, MD, H. Buschke, MD, C.A. Derby, PhD, and R.B. Lipton, MD

From the Saul R. Korey Department of Neurology (M.E.Z., M.J.K., J.V., H.B., C.A.D., R.B.L.), Albert Einstein College of Medicine, Bronx, NY; and Department of Neurosurgery (J.W.P., H.P.H.), Yale University School of Medicine, New Haven, CT.

Abstract

Background—Characterization of the behavioral correlates of neuromorphometry and neurochemistry in older adults has important implications for an improved understanding of the aging process. The objective of this study was to test the hypothesis that a measure of hippocampal neuronal metabolism was associated with verbal memory in nondemented older adults after controlling for hippocampal volume.

Methods—4-T MRI, proton magnetic resonance spectroscopy (^1H MRS), and neuropsychological assessment were conducted in 48 older adults (23 women; mean age 81 years). Average hippocampal *N*-acetyl aspartate/creatine ratios (NAA/Cr) and hippocampal volumes were obtained. Neuropsychological evaluation included tests of verbal memory (Buschke and Grober Free and Cued Selective Reminding Test–Immediate Recall [FCSRT-IR], Wechsler Memory Scale–Revised Logical Memory subtest) and attention and executive function (Trail Making Test Parts A and B).

Results—Linear regression analysis indicated that after adjusting for age, hippocampal NAA/Cr was a significant predictor of FCSRT-IR performance ($\beta = 0.38$, $p = 0.01$, $R^2 = 0.21$). Hippocampal volume was also a significant predictor of FCSRT-IR performance after adjusting for age and midsagittal area ($\beta = 0.47$, $p = 0.01$, $R^2 = 0.24$). In a combined model, hippocampal NAA/Cr ($\beta = 0.33$, $p = 0.03$) and volume ($\beta = 0.35$, $p = 0.03$) were independent predictors of FCSRT-IR performance, accounting for 30% of the variance in memory.

Conclusions—These findings indicate that nondemented older adults with smaller hippocampal volumes and lower levels of hippocampal *N*-acetyl aspartate/creatine ratio metabolites perform more poorly on a test of verbal memory. The integrity of both the structure and metabolism of the hippocampus may underlie verbal memory function in nondemented elderly.

With advancing age, healthy adults exhibit decline in verbal memory abilities^{1,2} and hippocampal volumetric decreases (e.g., see references^{3–6}) that are modestly associated (for review, see reference⁷). Additionally, metabolic markers of aging have been identified using proton MRS, which probes neuronal chemical function through examination of neurotransmitters. Decreased *N*-acetyl aspartate and its ratio to creatine (NAA/Cr) is a robust age-associated finding in the hippocampus.^{8–10}

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Address correspondence and reprint requests to Dr. Molly E. Zimmerman, Albert Einstein College of Medicine, Saul R. Korey Department of Neurology, 1165 Morris Park Ave., Room 343, Bronx, NY 10461 mzimmerm@aeom.yu.edu.

Disclosure: The authors report no conflicts of interest.

Because changes in neuronal metabolism precede cell death and volume loss, hippocampal NAA/Cr measures may supplement volumetric measures for the prediction of memory performance. One study⁸ examining this relationship reported that normal aging is associated with changes in hippocampal structure and neurochemistry, and that these changes may impact performance on tasks of spatial memory. The goal of the current study is to expand these findings by evaluating magnetic resonance (MR-)–derived hippocampal volumes and hippocampal NAA/Cr metabolites as predictors of verbal memory performance in a community-based sample of healthy older adults. We hypothesized that anatomic (hippocampal volume) and metabolic (hippocampal NAA/Cr) measures would be independent predictors of verbal memory performance in nondemented elderly.

METHODS

Participants

Between February 2004 and August 2006, a subset of 48 older adults was drawn from the Einstein Aging Study (EAS), a community-based sample of individuals over the age of 70 years residing in the Bronx, New York. Because the primary objective of this investigation was to examine MR-derived predictors of memory function in nondemented elderly, the subset was systematically selected to obtain a range of memory performance on the Buschke and Grober Free and Cued Selective Reminding Test–Immediate Recall (FCSRT-IR; discussed further below) in older adults who did not meet diagnostic criteria for dementia based on the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition.¹¹ In the absence of contraindications to MRI, all individuals with mild memory impairment (free recall FCSRT-IR ≤ 24 , $n = 14$) and a random sample of individuals with normal memory (free recall FCSRT-IR > 24 , $n = 34$) were invited to participate in the current study. FCSRT-IR free recall impairment cut-scores were derived from prior analyses.^{12,13} Of the 48 participants in the study, 8 reported a subjective memory complaint as determined by a positive response to the item “Do you feel that you have more problems with memory than most?” from the Geriatric Depression Scale.¹⁴ Of these participants with memory complaints, 6 exhibited memory within normal limits, and 2 exhibited mild memory impairment; therefore, 2 of the 48 participants in this sample met diagnostic criteria for amnesic mild cognitive impairment (MCI).¹⁵

The study design and methods of the EAS are described elsewhere.¹⁶ Briefly, potential participants were recruited through systematic sampling from Medicare or voter registration lists for Bronx County. Participants were excluded who reported severe sensory loss or medical conditions that would interfere with completion of neuropsychological assessment, were non-English speakers, or who were institutionalized. General cognitive status was assessed with the Blessed Information–Memory–Concentration test (BIMC¹⁷). Participants were evaluated at a diagnostic case conference attended by a study neurologist, neuropsychologist, and social worker.

Magnetic resonance imaging

MRI was performed on a Varian-Magnex 4-T imaging system at the Gruss Magnetic Resonance Research Center at the Albert Einstein College of Medicine, Bronx, New York. T1-weighted inversion recovery gradient echo images were acquired with 1.5-mm slice thickness, field of view (FOV) = 240, and 160×160 resolution, resulting in pixel resolution of $1.5 \times 1.5 \times 1.5$ mm³. Using planum temporale geometry, 120 slices were taken parallel to the planum temporale, resulting in 180-mm coronal–axial coverage. The images were reformatted orthogonal to the planum temporale, and volumetric measurements of the hippocampus were performed.^{18,19} The limit of the posterior hippocampal tail was identified from the oblique coronal image, wherein the crus of the fornix was visualized. Anteriorly, the pes hippocampus was disarticulated from the amygdala by identification of the alveus, or by extending the

horizontal line defined by the uncus recess of the temporal horn. Laterally and superiorly, the temporal horn CSF demarcated the hippocampus. Medially, the uncus and ambient cistern were used. Inferiorly, the subiculum was separated from the parahippocampal gray matter with a straight line. The intracranial midsagittal area was obtained to account for individual differences in head size.²⁰ Volumetrics were obtained by a single trained rater with high intrarater reliability (intraclass correlation coefficient = 0.99).

Magnetic resonance spectroscopy

All data were acquired at 4-T using a Varian INOVA console and quadrature head coil using a modified LASER sequence (10-mm thickness, 80 × 100-mm in-plane FOV selection) in combination with two dimensions of phase encoding (24 × 24, FOV = 192 × 192 mm, 19.2 minutes) angulating the plane along the temporal pole.²¹ The magnetic field homogeneity was adjusted for each subject.²² To provide reproducible selection criteria, hippocampal voxels were reconstructed using a voxel shifting method.^{23,24} Centers of reconstructed spectroscopic voxels were defined from structural images using anatomically defined criteria. Hippocampal boundaries were manually delineated on anatomic images, and a midline between the medial and lateral boundaries was calculated. Four loci—one positioned at the level of the aqueduct along the midline, two anterior loci, and one posterior locus—were selected by translating along the midline in 9-mm increments. These coordinates were used in voxel shifting reconstruction to provide spectroscopic voxels centered over these loci. Spectral data were obtained using a convolution difference of 250 Hz followed by 3 Hz of gaussian broadening and Fourier transformation in the spectral domain. Data were fit using gaussian line shapes, and the NAA/Cr ratio was determined by using the ratios of the resonance areas.

Neuropsychological evaluation

Based on the hypotheses of the current study, two verbal memory variables of interest were selected from the EAS comprehensive neuropsychological battery: free recall from the FCSRT-IR^{25,26} and immediate recall from the Wechsler Memory Scale–Revised Logical Memory subtest (LM).²⁷ The FCSRT-IR is a verbal memory task that controls attention and strategy use to maximize learning and provide a measurement of immediate memory that is not confounded by deficits in other cognitive abilities. In the first part of the task, participants name 16 objects that are displayed individually. They are then presented with the same 16 objects and asked to identify each object following a categorical prompt. In the *free recall* condition, a measure of self-organized retrieval, the participant is immediately asked to recall the 16 objects. If the participant does not correctly recall an object, he or she is provided with a category cue to test *cued recall*. There are a total of three free and cued recall trials; scores range from 0 to 48.

LM²⁷ is a verbal memory test in which participants are read two contextually related short stories and asked to recall story details. Scores range from 0 to 50.

The Trail Making Test²⁸ was examined to determine the specificity of cognitive findings. TMTA is a measure of attention involving psychomotor speed and visual scanning, whereas TMTB is a measure of executive function involving set shifting and concept formation. Scores for TMTA and TMTB are provided as seconds to task completion.

Statistical analyses

Age, education, and sex, were examined as potential covariates using Pearson product–moment and Spearman rank correlation coefficients. Ethnicity was examined as a potential covariate using analysis of variance. Pearson correlation coefficients were used to examine relationships among verbal memory performance, hippocampal volume, and hippocampal NAA/Cr.

A series of linear regression analyses were performed to examine MR-derived predictors of verbal memory performance. The first linear regression examined the effect of hippocampal volume on verbal memory performance with age and midsagittal area as covariates. The second linear regression analysis examined the effect of hippocampal NAA/Cr on verbal memory performance with age as a covariate. The third linear regression analysis examined the effect of both hippocampal neurochemistry and volume on verbal memory performance with age as a covariate. Linear regressions were repeated with measures of attention and executive function as dependent variables to examine specificity of the findings.

Secondary analyses were performed to examine the potentially spurious inclusion of individuals with mild memory impairment in our sample. Discriminant function analysis was used to determine the extent to which memory group membership could be predicted by hippocampal volume and NAA/Cr values. Pearson correlation coefficients were performed to explore the relationship between memory and MR-derived variables of interest in individuals exhibiting normal memory and individuals exhibiting mild memory impairment.

RESULTS

Sample characteristics

Sample demographics, verbal memory performance, and hippocampal measurements are presented in table 1. Sex and ethnicity characteristics were consistent with those of both the larger EAS cohort and the US Census Bureau data for Bronx County. Participants performed in the average range on verbal memory tests.^{29,30} There were no ethnicity differences on the MR-derived or memory variables of interest.

Separate left and right measurements were acquired for both hippocampal NAA/Cr and volume. There were no laterality differences in hippocampal NAA/Cr [$t(1,47) = 0.09, p = 0.93$] or volume [$t(1,38) = -0.17, p = 0.85$]; therefore, all left and right variables were combined (volumes) or averaged (NAA/Cr) to reduce the number of statistical comparisons. MRI-derived hippocampal volumetric and midsagittal area measurements were available for 39 and 36 individuals due to scan acquisition limitations. There were no differences in age, education, BIMC, memory performance, or hippocampal NAA/Cr between those participants who had hippocampal volumetric data and those that did not (data not shown).

Simple correlations

Pearson correlation coefficients revealed that age was associated with hippocampal volume ($r = -0.35, p < 0.03$); the strength of this relationship was similar after control of the midsagittal area ($r = -0.30, p < 0.08$). Individuals with smaller hippocampal volumes performed more poorly on the FCSRT-IR ($r = 0.45, p < 0.01$; figure 1). Individuals with lower hippocampal NAA/Cr also exhibited poorer verbal memory performance ($r = 0.43, p < 0.01$; figure 2). Finally, individuals with smaller hippocampal volumes exhibited lower NAA/Cr ($r = 0.32, p < 0.05$; figure 3). Education and sex were not associated with the primary variables of interest, with the exception of a relationship between education and LM ($r = 0.39, p < 0.01$).

Hippocampal volume and verbal memory

The model of the prediction of FCSRT-IR by hippocampal volume controlling for age and midsagittal area [$F(3,32) = 3.33, p < 0.03, R^2 = 0.24$] revealed a significant effect for hippocampal volume ($\beta = 0.47, t = 2.86, df = 32, p < 0.01$). The model for the prediction of LM performance was not significant.

Hippocampal NAA/Cr and verbal memory

The model of the prediction of FCSRT-IR performance by hippocampal NAA/Cr controlling for age [$F(2,45) = 5.90, p < 0.01, R^2 = 0.21$] revealed a significant effect for hippocampal NAA/Cr ($\beta = 0.38, t = 2.78, df = 45, p < 0.01$). The model for the prediction of LM performance was not significant.

Hippocampal NAA/Cr, hippocampal volume, and verbal memory

The model of the prediction of FCSRT-IR performance by hippocampal NAA/Cr and volume ($F_{(3,35)} = 5.05, p < 0.01, R^2 = 0.30$) revealed significant effects for both hippocampal NAA/Cr ($\beta = 0.33, t = 2.22, df = 35, p < 0.03$) and volume ($\beta = 0.35, t = 2.21, df = 35, p < 0.03$). The model for the prediction of LM performance was not significant. Table 2 depicts a summary of all three regression models for the prediction of FCSRT-IR.

Specificity of memory findings

Replication of analyses with measures of attention and executive function as dependent variables revealed nonsignificant models.

Memory impairment

As described previously, 34 participants exhibited normal memory performance and 14 participants exhibited mild memory impairment. Of the 14 mildly memory-impaired individuals, 2 reported a memory complaint and met diagnostic criteria for amnesic MCI.¹⁵ Linear regressions were repeated with the removal of the MCI participants, and results remained unchanged. Discriminant function analysis revealed a significant model for the prediction of memory group by hippocampal volume and NAA/Cr (Wilks lambda = 0.80, $p < 0.02$). The unstandardized canonical discriminant function coefficient was 3.46 for hippocampal NAA/Cr and 0.001 for hippocampal volume with a constant of -7.39 . Classification results indicated that 71.8% of individuals were correctly classified by memory group by hippocampal volume and NAA/Cr: 72.4% of the participants with normal memory and 70.0% of the participants with mild memory impairment. Pearson correlation analyses indicated that poorer verbal memory performance was associated with lower hippocampal NAA/Cr ($r = 0.38, p < 0.03$) and smaller hippocampal volumes ($r = 0.42, p < 0.03$) in elderly individuals with normal memory performance. However, there was no relationship between memory performance and hippocampal NAA/Cr ($r = -0.19, p < 0.51$) or volume ($r = -0.35, p < 0.40$) in participants with mild memory impairment.

DISCUSSION

The goal of this study was to examine hippocampal neuromorphometric and neurochemical predictors of verbal memory performance in a well-characterized sample of nondemented older adults. Our findings indicate that poorer performance on a cued list-learning verbal memory test was associated with smaller hippocampal volumes and lower levels of hippocampal NAA/Cr. When considered in concert, both measurements of hippocampal volume and neurochemistry were independent predictors of verbal memory that accounted for 30% of the variance in memory performance. This finding suggests that both the structural and metabolic integrity of the hippocampus support declarative memory abilities in nondemented elderly and that each of these biologic measures uniquely strengthens the ability to predict verbal memory performance. Further, these results seem to be specific to verbal memory performance as measured by the FCSRT-IR, because hippocampal volume and NAA/Cr were not significantly related to other cognitive measures of attention or executive function.

Investigations of the relationship between MRI-derived hippocampal volumes and memory performance have yielded modest associations in healthy older adult samples (for review, see references ⁷ and ³¹). In our sample of nondemented older adults, we demonstrate a relationship between hippocampal volume and performance on FCSRT-IR; individuals with smaller hippocampal volumes exhibited poorer free recall on a test of verbal memory. In addition, several studies have reported relationships between hippocampal metabolic markers of neuronal integrity and performance on navigational tasks.⁸ Previous studies have also demonstrated that medial temporal lobe metabolic markers are correlated with lower verbal memory performance in individuals with mild memory impairment³² and increase after memory training in healthy older adults.³³ Our findings indicated that nondemented older adults with lower NAA/Cr exhibited poorer free recall on a test of verbal memory.

Previous studies^{10,34} have reported relationships between brain metabolites and brain volume in the elderly, yet only one⁸ has specifically examined the relationship among age-related memory performance and the neurochemistry and volume of the hippocampus. The authors reported that older adults demonstrated decreased volumes, lower NAA/Cr, and poorer performance on tests of spatial memory and configural learning. Better performance on cognitive tasks was significantly associated with hippocampal volume and NAA/Cr. In addition, NAA/Cr was a significant predictor of spatial memory, whereas NAA/Cr and hippocampal volume were significant predictors of configural learning. In the current study, we examined a larger sample of older adults and performance on a verbal memory measure and found that both hippocampal volume and hippocampal NAA/Cr are significant predictors of performance on a verbal memory task. These findings both support and extend those of the aforementioned study,⁸ suggesting that both hippocampal structure and function support declarative memory processes in nondemented older adults.

Additional discussion should be given to the specificity of our finding that hippocampal volume and NAA/Cr were related to performance on one measure of immediate verbal memory, FCSRT-IR, but not another, LM. This finding may be unexpected given the classic view of the hippocampus as supportive of delayed memory rather than immediate memory performance (e.g., see reference ³⁵). The FCSRT-IR is a unique memory test that uses controlled attention and information processing to maximize learning.^{36,37} FCSRT performance has been shown to have high discriminative validity for the diagnosis of dementia (e.g., see reference ³⁸) and for prediction of the development of future dementia.¹² LM, conversely, uses an oral presentation of a short story to examine the contribution of a meaningful context to an individual's ability to learn and retrieve verbal information.^{27,37} Although both tasks are measures of immediate declarative verbal memory, the FCSRT-IR provides a measure of memory that is not confounded by potential difficulties in attention or executive function. It is notable that we observed consistently significant findings in performance on free recall of the FCSRT-IR, but not LM, because this may provide additional information regarding the complex nature of hippocampal structure and function relationships. Our findings suggest that hippocampal volume and NAA/Cr are predictors of performance on a cued list-learning verbal memory task that controls for attention and strategy use, but not of performance on a verbal memory test of contextually related information.

There are several limitations to the current study. Our MR scanning protocol focused on the examination of hippocampal volumetry and NAA/Cr. Thus, the neuroanatomic specificity of our findings cannot be determined with the design of our study. Similarly, our sample was drawn from a larger study of communitydwelling older adults, and we were not able to examine the relationship among our variables of interest across the entire adult lifespan or in individuals with clinical diagnoses (e.g., dementia). An important consideration for future investigations is that it is possible that the observed associations may vary as a function of both age and cognitive status. Finally, our sample comprised elderly individuals with both normal memory

performance and mild memory impairment. Additional analyses examining potential confounds associated with the clinical heterogeneity of our sample indicated that whereas significant associations between verbal memory performance and MR-derived hippocampal measures remained evident in individuals with normal memory, there were no relationships between these variables in the memory-impaired group. It is possible that the lack of a relationship between these variables in the latter group is due to truncated ascertainment of group membership, which likely resulted in diminished variability in memory performance. Nonetheless, this pattern of results lends confidence to the interpretation of our findings in the larger sample of nondemented elderly and suggests that the observed relationships were not simply an artifact of memory group status. Additional investigation is imperative to further characterize the complex relationships between memory performance and its biologic substrates across the spectrum of healthy, preclinical, and pathologic aging.

GLOSSARY

BIMC, Blessed Information-Memory-Concentration test
 CDR, Clinical Dementia Rating scale
 EAS, Einstein Aging Study
 FCSRT-IR, Buschke and Grober Free and Cued Selective Reminding Test–Immediate Recall
 FOV, field of view
 LM, Wechsler Memory Scale–Revised Logical Memory subtest
 MCI, mild cognitive impairment
 MR, magnetic resonance
 MRS, magnetic resonance spectroscopy
 NAA/Cr, *N*-acetyl aspartate/creatine ratio
 TMTA, Trail Making Test Part A
 TMTB, Trail Making Test Part B

ACKNOWLEDGMENT

The authors thank Charlotte Magnotta for assistance with participant recruitment; Danielle Coyle, Betty Forro, Alicia Gomez, and Mary Joan Sebastian for assistance with neuropsychological assessment; Cynthia Pan for assistance with hippocampus volumetric quantification; and all of the study participants who gave their time in support of this research.

Supported by National Institute on Aging Grant AG03949.

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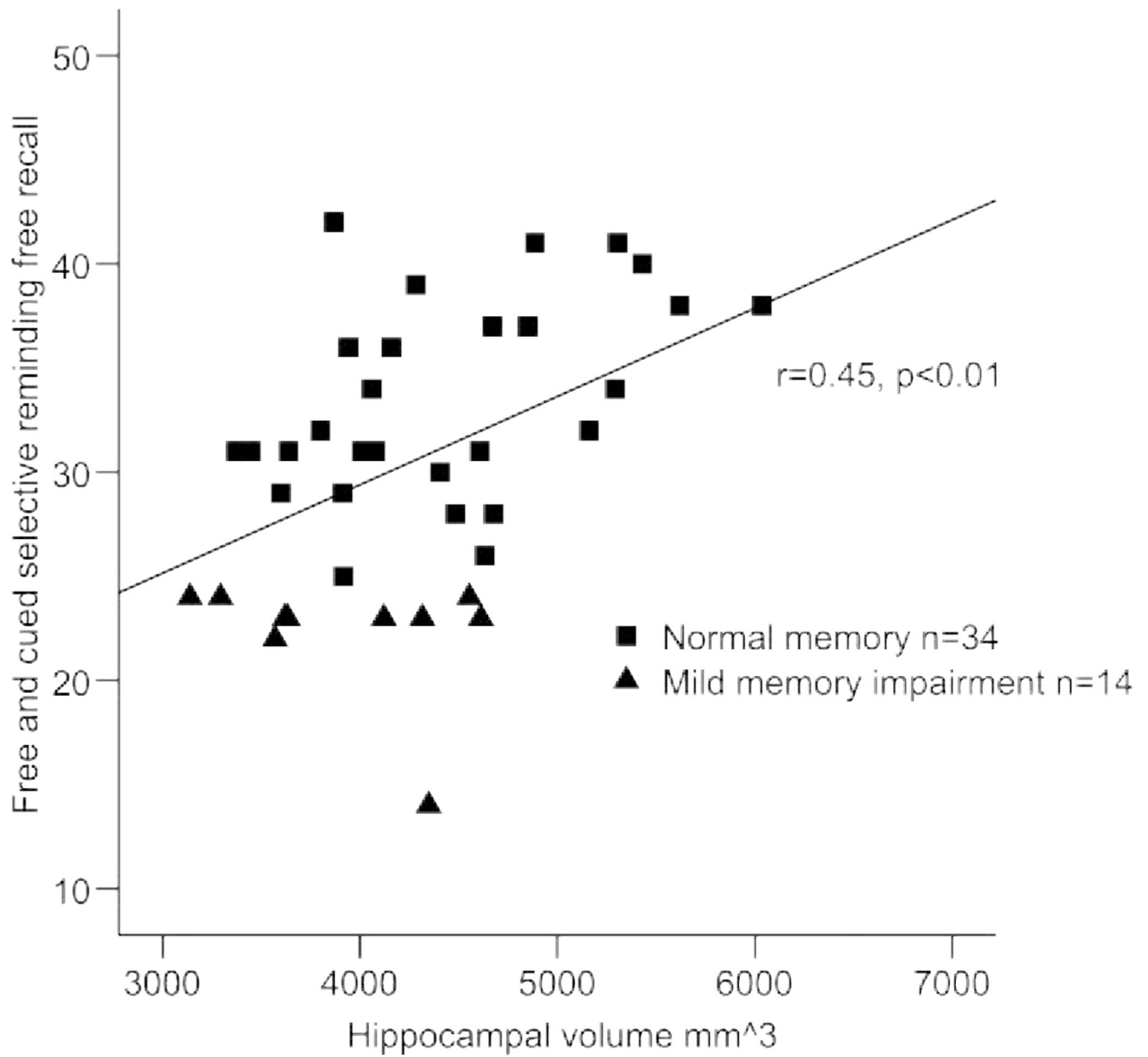


Figure 1.
Hippocampal volume and verbal memory performance in nondemented elderly

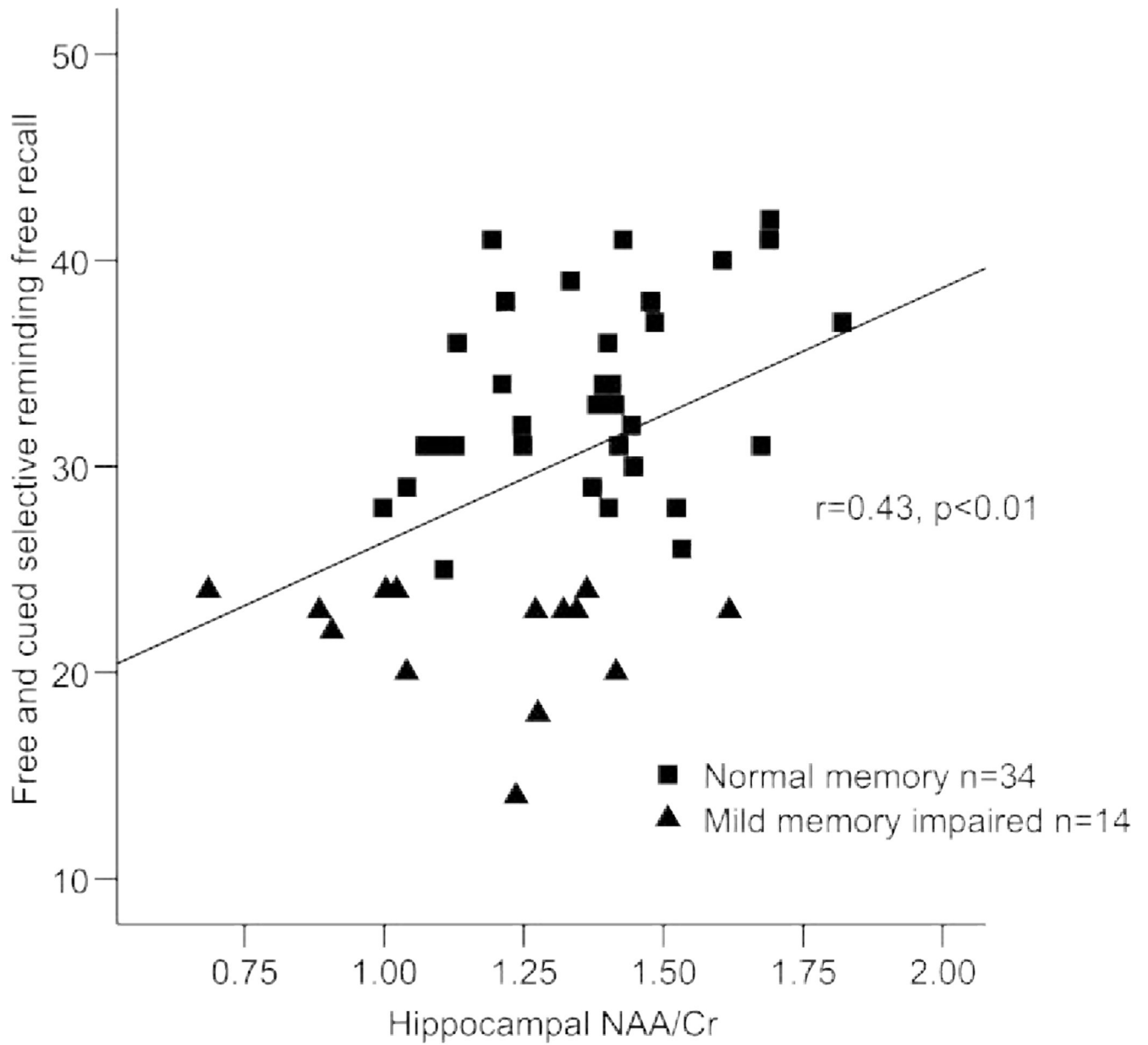


Figure 2. Hippocampal *N*-acetyl aspartate/creatinine ratio (NAA = CR) and verbal memory performance in nondemented elderly

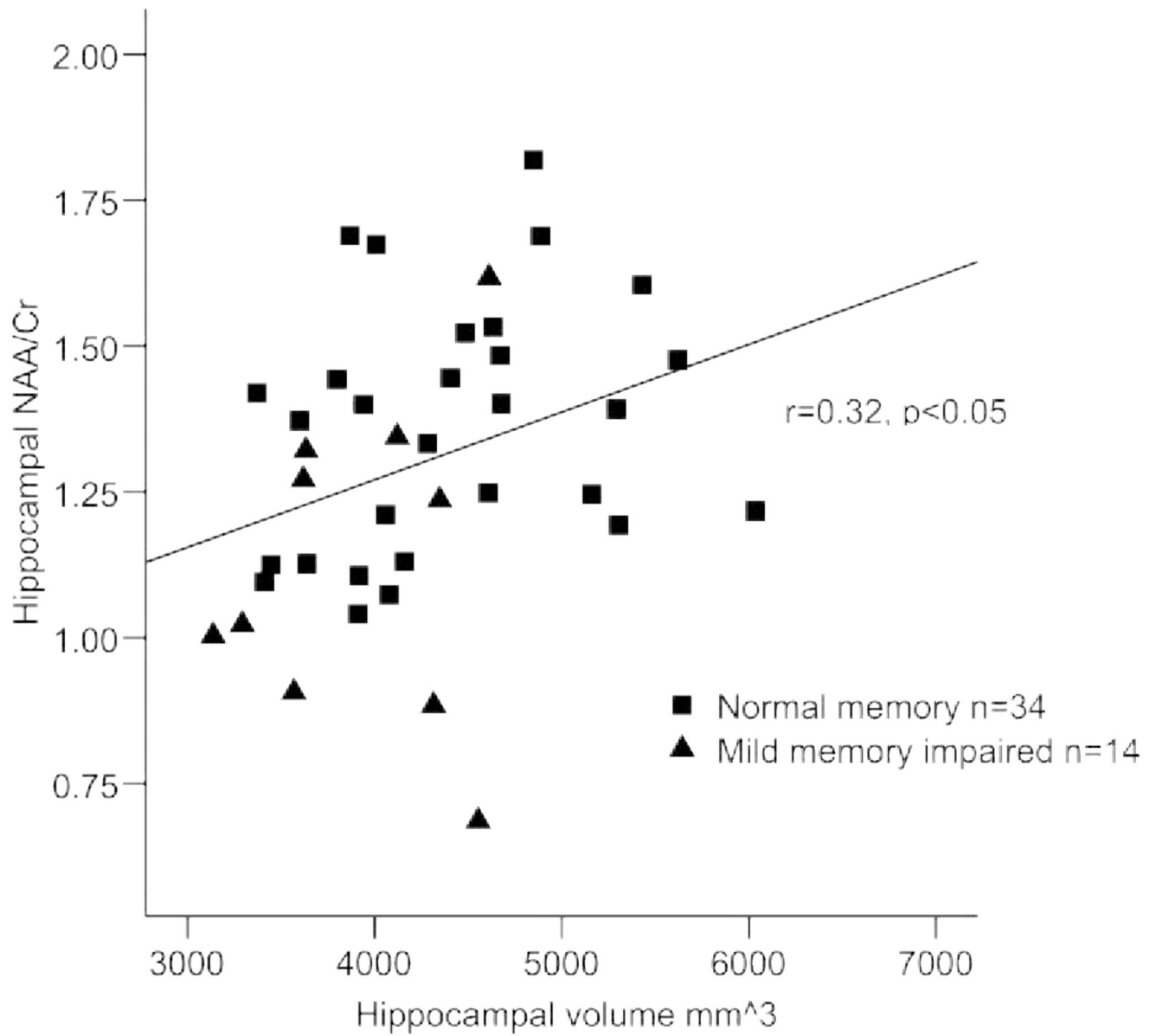


Figure 3. Hippocampal volume and *N*-acetyl aspartate/creatine ratio (NAA = CR) in nondemented elderly

Table 1

Sample demographics, verbal memory performance, and hippocampal measurements

	Total sample, n = 48	Normal memory, n = 34	Mild memory impairment, n = 14
Age, mean (SD), y	81.18 (5.47)	80.37 (5.77)	83.14 (4.2)
% Women	47.9	55.9	28.6
% White	72.9	73.5	71.4
Education, mean (SD), y	13.08 (3.11)	13.2 (3.50)	12.7 (1.90)
% Right-handed *	97.8	97.1	100
BIMC total errors, median (range)	2.00 (0–13)	2.00 (0–6)	3.5 (0–13)
CDR score, median (range)	0 (0–1)	0 (0–0.5)	0.5 (0–1)
FCSRT-IR free recall score, mean (SD)	30.06 (6.80)	33.47 (4.65)	21.79 (2.89)
FCSRT-IR total recall score, mean (SD)	47.73 (1.22)	47.94 (0.34)	47.21 (2.15)
LM total score, mean (SD)	18.02 (7.17)	19.7 (7.13)	14.43 (6.01)
Hippocampal volume, mean (SD) [†]	4.27 (0.07)	4.40 (0.07)	3.92 (0.01)
Hippocampal NAA/Cr, mean (SD)	1.30 (0.23)	1.36 (0.82)	1.17 (0.93)

MRI volumetric data are given in cubic centimeters.

* Handedness data available for n = 45.

[†] Hippocampal volumetric data available for n = 39.

BIMC = Blessed Information–Memory–Concentration test, total error score; CDR = Clinical Dementia Rating scale; FCSRT-IR = Buschke and Grober Free and Cued Selective Reminding Test–Immediate Recall; LM = Wechsler Memory Scale–Revised Logical Memory immediate recall stories A and B; NAA/Cr = *N*-acetyl aspartate/creatine ratio.

Table 2

Regression models for the effect of age, hippocampal volume, and hippocampal NAA/Cr on Free and Cued Selective Reminding Test free recall performance

Model no.	Predictor	R ²	Standardized β	p Value
1	Age	0.24	0.00	0.99
	Midsagittal area		0.10	0.55
	Hippocampal volume		0.47	0.01 [†]
2	Age	0.21	-0.17	0.23
	Hippocampal NAA/Cr		0.38	0.01 [†]
3	Age	0.30	0.01	0.96
	Hippocampal volume		0.35	0.03*
	Hippocampal NAA/Cr		0.33	0.03*

* Significant at the $p < 0.05$ level.

[†] Significant at the $p < 0.01$ level.

NAA/Cr = *N*-acetyl aspartate/creatine ratio.